

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reissue Application of : Box: REISSUE
Gervais DIONNE et al. : Group Art Unit: Not yet assigned
Original Patent No. 5,538,975
Serial No.: Not Yet Issued : Examiner: James O. Wilson
Filed: Herewith :
For: **1,3-OXATHIOLANE NUCLEOSIDE ANALOGUES AND METHODS FOR
USING SAME**

TRANSMITTAL OF REISSUE APPLICATION

Assistant Commissioner for Patents
Washington, D.C. 20231

SIR:

Transmitted herewith is an application for reissue of U.S. Patent No. 5,538,975, originally issued on July 23, 1996.

U.S. Patent No. 5,538,975 is currently involved in Interference No. 104,333.

Concurrently with the filing of this reissue application, counsel for applicants are filing a motion to have this reissue application added to Interference No. 104,333.

The application seeks reissue of the patent with amendments to add claims to provide protection for subject matter narrower in scope than that of the presently claimed subject matter. In addition, the reissue seeks to correct the inventorship from Gervais Dionne to Gervais Dionne, Bernard Belleau, Nghe Nguyen-Ba, and Boulos Zacharie. Further, the reissue seeks to amend the specification to claim benefit under 35 U.S.C. §120 of prior copending application Serial No. 07/564,160, filed August 8, 1990.

The subject matter sought to be claimed in new claims 6-68 is of an intermediate scope or is described using alternative wordings of existing patent claims. Thus, this reissue application does not seek to broaden the scope of patent protection.

New claims 6-9 are dependent upon claim 1 and further define the pharmaceutically acceptable esters. Support for new claims 6-9 can be found in the specification at column 2, line 8-32.

New claim 10 recites that the compound of claim 1 is the specified (-)-enantiomer or a pharmaceutically acceptable salt thereof. Support for claim 10 is provided, for example, by the disclosure at column 1, lines 43-65.

Claim 11 recites specific pharmaceutically acceptable salts of claim 10. Support for claim 11 can be found at column 2, lines 33-47.

Claim 12 recites the specified (-)-enantiomer and is supported throughout the disclosure. See, for example, column 1, lines 50-52. Claims 13-19 are similar to claims 6-12, respectively, except that they depend from claim 2 rather than claim 1. Claims 13-19 are supported in the disclosure; see, for example, the portions of the disclosure cited for the support of claims 6-12.

Claims 20-26 also correspond to claims 6-12, respectively, except that they depend from claim 3, rather than claim 1. Claims 20-26 are supported in the disclosure; see, for example, the portions of the disclosure cited above with respect to claims 6-12.

Claims 27-33 are also similar to claims 6-12, respectively, except that they depend from claim 4, rather than claim 1. Claims 27-33 are supported in the disclosure; see, for example, the portions of the disclosure cited above with respect to claim 6-12.

Claim 34 is an alternative recitation to claim 2. Claim 2 recited the subject matter as being a compound having a specified purity in terms of a maximum amount of corresponding (+)-enantiomer present. Claim 34 recites a composition containing the (-)-enantiomer and the corresponding (+)-enantiomer wherein the (+)-enantiomer has a specified maximum limit. Claims 35-41 further define the components of the composition of claim 34. These claims are supported by the disclosure; see, for example, the portions of the disclosure cited above with regards to claims 6-12.

Claims 42-57 further define the maximum amount of corresponding (+)-enantiomer in the composition of claim 34. These claims are supported by the disclosure at, for example, column 1, lines 55-59. See also patent claims 3-4.

Claims 58-60 further define the amount of compound present in the composition of claim 5. These claims are supported by the disclosure; see, e.g., column 3, lines 44-47. Claim 61 recites a pharmaceutical composition corresponding to that of claim 5 except that claim 61 is dependent upon claims 6-57, rather than claims 1-4. Support for claim 61 is

provided within the disclosure at, for example, column 3, lines 64-column 4, line 4. See also patent claim 5.

Claims 62-64 further specify the amount of compound in the composition of claim 61. Support for claims 62-64 is to be provided at column 3, lines 44-47.

Thus, new claims 4-33 and 58-60 are each dependent upon one of patent claims 1-5 and recite subject matter narrower in scope than the patent claims. Claim 34 is an alternative recitation to patent claim 2. The claims dependent upon claim 34, i.e., claims 35-57 and 65-68 further define aspects of the composition of claim 34. Claims 61-64 recite compositions like that of claim 5 but instead depend on claims 6-57.

Applicants believe their original patent U.S. Patent No. 5,538,975 to be wholly or partly inoperative by reason of failing to include claims of intermediate scope. Such claims of intermediate scope provide a "hedge" against possible invalidity arguments that might be brought by other parties. ("The narrower appealed claims are simply a hedge against possible invalidity of the original claims should the prior use be proved, which is a proper reason for asking that a reissue be granted." *In re Handel*, 136 U.S.P.Q. 460 (CCPA 1963), footnote 2; commented upon with approval in *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 11 U.S.P.Q.2d 1750 (Fed. Cir. 1989)).

Applicants also believe that their patent is partly inoperative in that it does not provide the requisite statement for purposes of priority under 35 U.S.C. §120 with respect to Serial No. 07/564,160. Applicants wish to perfect this priority by amending the specification to include a reference to the '160 application, pursuant to 35 U.S.C. §120.

Further, applicants believe that their patent is partly inoperative in that it fails to indicate the correct inventive entity. A petition to correct inventorship under 35 U.S.C. §1.324 was filed in US 5,538,975 on March 3, 1993. This petition sought correction of the inventive entity from Gervais Dionne to Gervais Dionne, Nghe Nguyen-Ba, Boules Zacharie, and Bernard Belleau. This corrected inventive entity (as well as the originally named inventive entity) is entitled to claim benefit under 35 U.S.C. §120, of previously filed copending application 07/564,160.

Prior to the declaration of Interference No. 104, 333, no action was taken on applicants' Petition to Correct Inventorship. After the Interference was declared, the APJ issued an Order on July 19, 2000, denying the Petition without prejudice. Specifically, the

APJ held that the Petition as filed could not be granted because there was no evidence filed with the Petition demonstrating that Pierrette Belleau was the executrix of the estate of Bernard Belleau, deceased. Concurrently with the filing of this Reissue application, applicants are filing a renewed Petition under 37 CFR §1.324, along with evidence demonstrating that Pierrette Belleau was the executrix of the estate of Bernard Belleau.

As for the requirement of at least one common inventor under 35 USC §120, firstly it is noted that original claim 10 of the '160 application recited, *inter alia*, *cis*-2-hydroxymethyl-5-(5'-fluorocytosin-1'-yl)-1,3-oxathiolane in the form of a racemic mixture or single enantiomer. Thus, the proper inventorship of the '160 application, as filed, necessarily encompasses the inventive entity of the '975 patent, whatever that inventive entity is, because the latter also claims a single enantiomer of the named compounds.

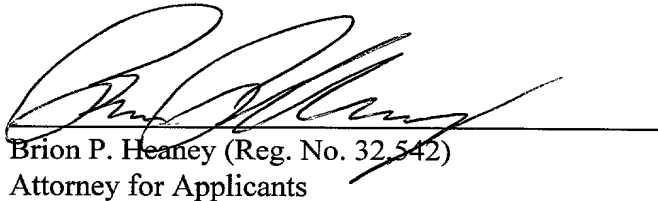
The '160 application as originally filed named Bernard Belleau, William L. Brown, Tarek Mansour, Allan Tse, Dilip Madhukas Dixit, Nghe Nguyen-Ba, and Boulos Zacharie as the inventive entity. Thus, it did not include Gervais Dionne, the originally named sole inventor of '975. However, the applicants are seeking to correct the inventive entity of '975 in the instant reissue application to Gervais Dionne, Nghe Nguyen-Ba, Boules Zacharie, and Bernard Belleau. When the petition is granted, there will be at least one common inventor between the instant reissue application and the '160 application. A common inventor will also exist if the petition were to be denied, i.e., if Dionne remains as sole inventor of '975. This is because, as explained below, a petition which changes the inventorship of '160 to include Dionne has been filed.

BioChem Pharma has taken steps to correct the inventorship in the '160 application to include Dionne as an inventor, via Serial No. 08/306,830, filed August 15, 1994, a continuation of the '160 application. On March 3, 1999, a Petition to Correct Inventorship was filed in Serial No. 08/306,830. The petition seeks to correct the inventorship to Bernard Belleau, Nghe Nguyen-Ba, Boulos Zacharie and Gervais Dionne. This also will effect the same change in the parent of '830, i.e., in '160. See MPEP §201.03, p. 200-8. Further, it is noted that the inventorship overlap requirement of 35 U.S.C. §120 need not be present on the date a continuing application is filed or when a parent application issues or becomes abandoned. See MPEP §201.03, page 200-7.

Submitted with this Transmittal are:

- A Declaration/Power of Attorney under 37 C.F.R. §1.63 and Reissue Declaration in Accordance with 37 C.F.R. §1.172 and §1.175 (unexecuted).
- A Written Consent of Assignee under 37 C.F.R. §1.172 and/or Offer to Surrender the Patent under 37 C.F.R. §1.178.
- The specification of the reissue application in accordance with 37 C.F.R. §1.173, amended to incorporate the corrections listed on the six page Certificate of Correction.
- A check in payment of the fees for this Reissue Application.

Respectfully submitted,



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Filed: November 29, 2000

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Approved for use through 12/30/2000. OMB 0651-0033
Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

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REISSUE APPLICATION FEE TRANSMITTAL FORM

Docket Number (Optional)
IAF-16-RE

Claims as Filed - Part 1

Claims in Patent	For	Number Filed in Reissue Application	(3) Number Extra	Small Entity		Other than a Small Entity	
				Rate	Fee	Rate	Fee
(A) 8 (C) 2	Total Claims (37 CFR 1.16(j)) Independent Claims (37 CFR 1.16(i))	(B) 98 (D) 3	**** 78 * 0	X\$18.00= X\$80.00=	\$1,404 =	or X\$ =	
Basic Fee (37 CFR 1.16(h))					\$710		\$
Total Filing Fee					\$2,114	OR	\$

Claims as Amended - Part 2

	(1) Claims Remaining After Amendment		(2) Highest Number Previously Paid For	(3) Extra Claims Present	Small Entity		Other than a Small Entity	
					Rate	Fee	Rate	Fee
Total Claims (37 CFR 1.16(j))	***	MINUS	**	*	X\$ =	or	X\$ =	
Independent Claims (37 CFR 1.16(i))	***	MINUS	*****	=	X\$ =		X\$ =	
Total Additional Fee					\$	OR	\$	

* If the entry in (D) is less than the entry in (C), Write "0" in column 3.

** If the "Highest Number of Total Claims Previously Paid For" is less than 20, Write "20" in this space.

*** After any cancellation of claims

**** If "A" is greater than 20, use (B - A); if "A" is 20 or less, use (B - 20).

***** "Highest Number of Independent Claims Previously Paid For" or Number of Independent Claims in Patent (C).

☒ A check in the amount of \$270.00 is attached for the multiple dependent fee.

☐ Please charge Deposit Account No. _____ in the amount of _____.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any additional fees under 37 CFR 1.16 or 1.17 which may be required, or credit any overpayment to Deposit Account No. 13-3402.
A duplicate copy of this sheet is enclosed.

☒ A check in the amount of \$ 2,114.00 to cover the filing / additional fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on form PTO-2038.

November 29, 2000

Date

Signature of Applicant, Attorney or Agent of Record

Brion P. Heaney, Reg. No. 32,542

Typed or printed name

JC914 U.S. PTO
09/726244

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reissue Application of : Box: REISSUE
Gervais DIONNE et al. : Group Art Unit: Not yet assigned
Original Patent No. 5,538,975
Serial No.: Not Yet Issued : Examiner: James O. Wilson
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For: **1,3-OXATHIOLANE NUCLEOSIDE ANALOGUES AND METHODS FOR
USING SAME**

WRITTEN CONSENT OF ASSIGNEE AND OFFER TO SURRENDER

Assistant Commissioner for Patents
Washington, D.C. 20231

SIR:

BioChem Pharma Inc. is the assignee of record of the entire rights and interests of U.S. Patent No. 5,538,975, issued July 23, 1996, as evidenced by the assignment recorded August 1, 1994 at Reel 7162/Frames 0534-0540 and the assignment recorded March 3, 1999, at Reel 9790/Frames 0633-0636.¹

The undersigned is an authorized officer of the assignee of record, BioChem Pharma Inc. The undersigned affirms that he has the power to consent to this reissue application on behalf of the recorded assignee. BioChem Pharma Inc. hereby consents to this reissue application in its entirety and offers to surrender the original patent.

In accordance with 37 C.F.R. §3.73(b), the undersigned authorized officer certifies that the Notice of Recordation of Assignment documents of the above-mentioned application and patent have been reviewed and that, to the best of assignee's knowledge and belief, record

¹In the interest of full disclosure, it is noted that Tanaud International B.V., a wholly-owned subsidiary of the assignee of record, has an interest in this patent by virtue of an unrecorded assignment. Tanaud International B.V. has authorized BioChem Pharma Inc. to hold and maintain this patent in the name of BioChem Pharma and to take all necessary action in the PTO. BioChem has the power to consent to this reissue since it is the Assignee of record and is the sole owner of Tanaud International B.V..

28. 11.00

Harold A. Lee

Title: Vice President Legal Affairs & General Counsel
of BioChem Pharma Inc.



US005538975A

United States Patent [19]

Dionne

[11] Patent Number: 5,538,975

[45] Date of Patent: Jul. 23, 1996

[54] 1,3-OXATHIOLANE NUCLEOSIDE
COMPOUNDS AND COMPOSITIONS

[75] Inventor: Gervais Dionne, Laval, Canada

[73] Assignee: BioChem Pharma, Inc., Laval, Canada

[21] Appl. No.: 190,203

[22] PCT Filed: Jul. 24, 1992

[86] PCT No.: PCT/CA92/00321

§ 371 Date: Feb. 1, 1994

§ 102(e) Date: Feb. 1, 1994

[87] PCT Pub. No.: WO93/03027

PCT Pub. Date: Feb. 18, 1993

[30] Foreign Application Priority Data

Aug. 1, 1991 [GB] United Kingdom 9116601

[51] Int. Cl.⁶ C07D 411/04; A61K 31/505[52] U.S. Cl. 514/256; 514/49; 514/50;
514/269; 514/274; 536/4.1; 544/242[58] Field of Search 536/4.1; 514/23,
514/24, 49, 274, 85, 256, 269; 544/242

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Jeong, et al. "Structure-Activity Relationships of β -D-(2S, 5R)- and α -D-(2S,5R)-1,3-Oxathiolanyl Nucleosides as Potential Anti-HIV Agents", *J. Med. Chem.*, vol. 36, pp. 2627-2638 (1993).

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Chang et al., *J. of Biol. Chemistry*, vol. 267, No. 31, pp. 22414-22420, Nov. 5, 1992.

Primary Examiner—James O. Wilson
Attorney, Agent, or Firm—Fish & Neave; James F. Haley, Jr.; Leslie A. McDonell

[57]

ABSTRACT

The invention relates to 1,3-oxathiolane nucleoside analogues and their use in the treatment of viral infections. More specifically, this invention relates to (-)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one and pharmaceutically acceptable derivatives and pharmaceutical formulations thereof.

5 Claims, No Drawings

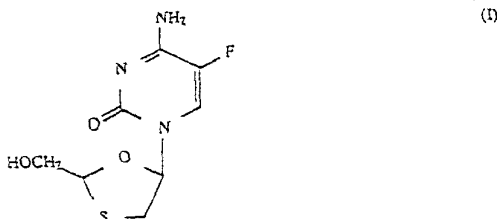
1,3-OXATHIOLANE NUCLEOSIDE COMPOUNDS AND COMPOSITIONS

This application is a continuation-in-part of copending application Serial No. 07/564,160, filed August 8, 1990, now abandoned.

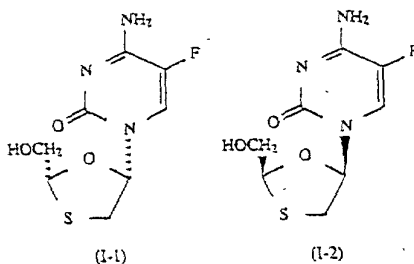
The present invention relates to nucleoside analogues and their use in medicine. More specifically the invention is concerned with 1,3-oxathiolane nucleoside analogues, pharmaceutical formulations thereof and the use thereof in the treatment of viral infections.

The only compound currently approved for the treatment of conditions caused by HIV is 3'-azido-3'-deoxythymidine (AZT, zidovudine, BW 509U). However, this compound has a significant side-effect liability and thus either cannot be employed or, once employed, may have to be withdrawn in a significant number of patients. There is in consequence a continuing need to provide compounds which are effective against HIV but with a concomitant significantly better therapeutic index.

The compound of formula (I)



is a racemic mixture of the two enantiomers of formulae (I-1) and (I-2):



We have now found that, surprisingly, the (-)-enantiomer of the compound of formula (I) is much more active than the (+)-enantiomer, although both enantiomers show unexpectedly low cytotoxicity. There is thus provided in a first aspect of the invention the (-)(or laevorotatory) enantiomer of the compound of formula (I) and pharmaceutically acceptable derivatives thereof.

The (-)-enantiomer has the chemical name (-)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (hereinafter compound (A)). This enantiomer has the absolute stereochemistry shown in formula (I-1).

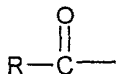
Preferably compound (A) is provided substantially free of the corresponding (+)-enantiomer, that is to say no more than about 5% w/w of the (+)-enantiomer, more preferably no more than about 2%, and most preferably less than about 1% w/w is present.

By "a pharmaceutically acceptable derivative" is meant any pharmaceutically acceptable salt, ester, or salt of such ester, of compound (A) or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) compound (A) or an antivirally active metabolite or residue thereof.

It will be appreciated by those skilled in the art that compound (A) may be modified to provide pharmaceutically

acceptable derivatives thereof, at functional groups in both the base moiety and at the hydroxymethyl group of the oxathiolane ring. Modification at all such functional groups are included within the scope of the invention. However, of particular interest are pharmaceutically acceptable derivatives obtained by modifications of the 2-hydroxymethyl group of the oxathiolane ring.

Preferred esters of compound (A) include the compounds in which the hydrogen of the 2-hydroxymethyl group is replaced by an acyl function



in which the non-carbonyl moiety R of the ester is selected from hydrogen, straight or branched chain alkyl (e.g., methyl, ethyl, n-propyl, t-butyl, n-butyl), alkoxyalkyl (e.g., methoxymethyl), aralkyl (e.g., benzyl), aryloxyalkyl (e.g., phenoxymethyl), aryl (e.g., phenyl optionally substituted by halogen, C₁₋₄ alkyl or C₁₋₄ alkoxy); sulphonate esters such as alkyl- or aralkylsulphonyl (e.g., methanesulphonyl); amino acid esters (e.g., L-valyl or L-isoleucyl) and mono-, di- or tri-phosphate esters.

With regard to the above described esters, unless otherwise specified, any alkyl moiety present advantageously contains 1 to 16 carbon atoms, particularly 1 to 4 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group.

In particular the esters may be a C₁₋₁₆ alkyl ester, an unsubstituted benzyl ester or a benzyl ester substituted by at least one halogen (bromine, chlorine, fluorine or iodine), C₁₋₆ alkyl, C₁₋₆ alkoxy, nitro or trifluoromethyl groups.

Pharmaceutically acceptable salts of the compound (A) include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic, toluene-p-sulphonic, tartaric, acetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic and benzenesulphonic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and NR₄⁺ (where R is C₁₋₄ alkyl) salts.

References hereinafter to a compound according to the invention include both the compound (A) and its pharmaceutically acceptable derivatives.

The compounds of the invention either themselves possess antiviral activity and/or are metabolizable to such compounds. In particular these compounds are effective in inhibiting the replication of retroviruses, including human retroviruses such as human immunodeficiency viruses (HIV's), the causative agents of AIDS.

The compounds of the invention are also useful in the treatment of animals including man infected with the hepatitis B virus (HBV).

There is thus provided as a further aspect of the invention compound (A) or a pharmaceutically acceptable derivative thereof for use as an active therapeutic agent in particular as an antiviral agent, for example in the treatment of retroviral infections or HBV infections.

In a further or alternative aspect there is provided a method for the treatment of a viral infection, in particular an infection caused by HBV or a retrovirus such as HIV, in a

There is also provided in a further or alternative aspect use of compound (A) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a viral infection.

The compounds of the invention are also useful in the prevention of progression to clinical illness of individuals who are anti-HIV antibody or HIV-antigen positive and in prophylaxis following exposure to HIV.

The compounds of the invention are also useful in the treatment of animals including man infected with the hepatitis B virus.

It will be further appreciated that the amount of a compound of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general however a suitable dose will be in the range of from about 0.1 to about 750 mg/kg of body-weight per day preferably in the range of 0.5 to 60 mg/kg/day, most preferably in the range of 1 to 20 mg/kg/day.

The compound is conveniently administered in unit dosage form; for example containing 10 to 1500 mg, conveniently 20 to 1000 mg, most conveniently 50 to 700 mg of active ingredient per unit dosage form.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising compound (A) or a pharmaceutically acceptable derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, option-

ally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

- 5 Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

- Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparation may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

- The compounds according to the invention may also be formulated for parenteral administration (e.g., by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation or sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

- For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

- Formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

- Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in

the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in moulds.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For intra-nasal administration the compounds of the invention may be used as a liquid spray or dispersible powder or in the form of drops.

Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilizing agents or suspending agents. Liquid sprays are conveniently delivered from pressurized packs.

For administration by inhalation the compounds according to the invention are conveniently delivered from an insufflator, nebulizer or a pressurized pack or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges or e.g., gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

When desired the above described formulations adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical compositions according to the invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

The compounds of the invention may also be used in combination with other therapeutic agents for example other anti-infective agents. In particular the compounds of the invention may be employed together with known antiviral agents.

The invention thus provides, in a further aspect, a combination comprising the compound (A) or a physiologically acceptable derivative thereof together with another therapeutically active agent, in particular an antiviral agent.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier therefor comprise a further aspect of the invention.

Suitable therapeutic agents for use in such combinations include acyclic nucleosides such as acyclovir or ganciclovir, interferons such as alpha, beta or gamma-interferon, renal excretion inhibitors such as probenecid, nucleoside transport inhibitors such as dipyridamole, 2',3'-dideoxynucleosides such as AZT, 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, 2',3'-dideoxythymidine, 2',3'-dideoxy-2',3'-didehydrothymidine and 2',3'-dideoxy-2',3'-didehydrocytidine, immunomodulators such as interleukin-2 (IL-2) and granulocyte macrophage colony stimulating factor (GM-CSF), erythropoietin, amphotericin, thymomodulin, thymopentin, foscarnet, ribavirin and inhibitors of HIV binding to CD4 receptors e.g., soluble CD4, CD4 fragments, CD4

hybrid molecules, glycosylation inhibitors such as 2-deoxy-D-glucose, castanospermine and 1-deoxynojirimycin.

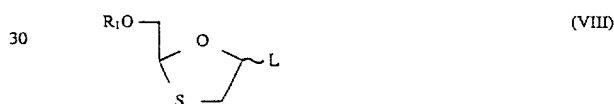
The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When the compound (A) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same virus the dose of each compound may be either the same as or differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

The compound (A) and its pharmaceutically acceptable derivatives may be prepared by any method known in the art for the preparation of compounds of analogous structure, for example as described in European Patent Publication 0382526 A2.

It will be appreciated by those skilled in the art that for certain of the methods described herein below the desired stereochemistry of the compound (A) may be obtained either by commencing with an optically pure starting material or by resolving the racemic mixture at any convenient stage in the synthesis. In the case of all the processes the optically pure desired product may be obtained by resolution of the end product of each reaction.

In one such process a 1,3-oxathiolane of formula (VIII)



wherein the anomeric group L is a displaceable group, is reacted with an appropriate base. Suitable groups L include —OR where R is an alkyl group, e.g., a C₁₋₆ alkyl group such as methyl or R is an acyl group, e.g., a C₁₋₆ alkyl group such as acetyl or halogen, for example iodine, bromine or chlorine.

The compound of formula (VIII) is conveniently reacted with 5-fluoro-cytosine or an appropriate pyrimidine base precursor thereof (previously silylated with a silylating agent such as hexamethyldisilazane) in a compatible solvent such as methylene chloride using a Lewis acid such as titanium tetrachloride, trimethylsilyltriflate, trimethylsilyl iodide (TMSI) or tin (IV) compound such as SnCl₄.

The 1,3-oxathiolanes of formula (VIII) may be prepared for example by reaction of an aldehyde of formula (VII) with a mercaptoacetal of formula (VI) in a compatible organic solvent, such as toluene in the presence of an acid catalyst for example a Lewis acid such as zinc chloride.



The mercaptoacetals of formula (VI) may be prepared by methods known in the art, for example G. Hesse and I. Jorder, *Chem. Ber.*, 85, pp. 924-932 (1952).

The aldehydes of formula (VII) may be prepared by methods known in the art for example E.G. Halloquist and H. Hibbert, *Can. J. Research*, 8, pp. 129-136 (1933). Conveniently the crude aldehyde (VII) may be purified by conversion to the crystalline bisulphite addition adduct and subsequent reconversion to the free aldehyde.

In a second process the compound (A) is obtained by base interconversion of a compound of formula (IX)



where B is a base convertible to 5-fluoro-cytosine. Such interconversion may be effected either by simple chemical transformation (e.g. the conversion of uracil base to cytosine) or by an enzymatic conversion using a deoxyribosyl transferase. Such methods and conditions for base interconversion are well known in the art of nucleoside chemistry.

In a third process a compound of formula (XI)



may be converted to the compound (A) by conversion of the anomeric NH_2 group to the 5-fluoro-cytosine base by methods well known in the nucleoside chemistry art.

Many of the reactions described hereinabove have been extensively reported in the context of nucleoside synthesis, for example in *Nucleoside Analogs-Chemistry, Biology and Medical Applications*, R. T. Walker et al., Eds., Plenum Press, New York (1979) at pages 165-192 and T. Ueda, *Chemistry of Nucleosides and Nucleotides*, Vol I, L.B. Townsend Ed., Plenum Press, New York (1988) at pages 1-112, the disclosures of which are incorporated by reference herein.

It will be appreciated that the above reactions may require the use of, or conveniently may be applied to, starting materials having protected functional groups, and deprotection might thus be required as an intermediate or final step to yield the desired compound. Protection and deprotection of functional groups may be effected using conventional means. Thus, for example, amino groups may be protected by a group selected from aralkyl (e.g. benzyl), acyl, aryl (e.g. 2,4-dinitrophenyl) or silyl; subsequent removal of the protecting group being effected when desired by hydrolysis or hydrogenolysis as appropriate using standard conditions. Hydroxyl groups may be protected using any conventional hydroxyl protecting group, for example, as described in *Protective Groups in Organic Chemistry*, J. F. W. McOmie, Ed., Plenum Press, New York (1973) or T. W. Greene, *Protected Groups in Organic Synthesis*, John Wiley and Sons, New York (1981). Examples of suitable hydroxyl protecting groups include groups selected from alkyl (e.g. methyl, t-butyl or methoxymethyl), aralkyl (e.g., benzyl, diphenylmethyl or triphenylmethyl), heterocyclic groups such as tetrahydropyranyl, acyl (e.g., acetyl or benzoyl) and silyl groups such as trialkylsilyl (e.g., t-butyldimethylsilyl). The hydroxyl protecting groups may be removed by conventional techniques. Thus, for example, alkyl, silyl, acyl and heterocyclic groups may be removed by solvolysis, e.g., by hydrolysis under acidic or basic conditions. Aralkyl groups such as triphenylmethyl may similarly be removed by solvolysis, e.g., by hydrolysis under acidic conditions. Aralkyl groups such as benzyl may be cleaved for example by treatment with BF_3 /etherate and acetic anhydride followed by removal of acetate groups so formed at an appropriate stage in the synthesis. Silyl groups may also conveniently be removed using a source of fluoride ions such as tetra-n-butylammonium fluoride.

In the above processes compound (A) is generally obtained as a mixture of the cis and trans isomers of which the cis isomer is the compound of interest.

These isomers may be separated by physical means, e.g., chromatography on silica gel or by fractional crystallization, either directly or on a suitable derivative thereof, e.g., acetates (prepared for example with acetic anhydride) followed, after separation, by conversion back to the parent product (e.g., by deacetylation with methanolic ammonia).

Pharmaceutically acceptable salts of the compounds of the invention may be prepared as described in U.S. Pat. No. 4,383,114, the disclosure of which is incorporated by reference herein. Thus, for example, when it is desired to prepare an acid addition salt of compound (A) the product of any of the above procedures may be converted into a salt by treatment of the resulting free base with a suitable acid using convention methods. Pharmaceutically acceptable acid addition salts may be prepared by reacting the free base with an appropriate acid optionally in the presence of a suitable solvent such as an ester (e.g., ethyl acetate) or an alcohol (e.g., methanol, ethanol or isopropanol). Inorganic basic salts may be prepared by reacting the parent compound with a suitable base such as an alcohol (e.g., methanol). Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compound (A) using conventional methods.

Compound (A) may be converted into a pharmaceutically acceptable phosphate or other ester by reaction with a phosphorylating agent, such as POCl_3 , or a suitable esterifying agent, such as an acid halide or anhydride, as appropriate. An ester or salt of compound (A) may be converted to the parent compound for example by hydrolysis.

Resolution of the final product, or an intermediate or starting material therefor may be effected by any suitable method known in the art: see for example E. L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw Hill (1962) and S. H. Wilen, *Tables of Resolving Agents*.

Thus for example the compound (A) may be obtained by chiral HPLC using a suitable stationary phase for example acetylated β -cyclodextrin or cellulose triacetate and a suitable solvent for example an alcohol such as ethanol or an aqueous solution of for example triethyl ammonium acetate. Alternatively the compounds may be resolved by enzyme mediated enantioselective catabolism with a suitable enzyme such as cytidine deaminase or selective enzymatic degradation of a suitable derivative using a 5'-nucleotidase. When resolution is effected enzymatically the enzyme may be employed either in solution or, more conveniently, in immobilized form. Enzymes may be immobilized by any method known in the art, for example by adsorption onto a resin such as Eupergit C.

The invention will be further described by the following examples which are not intended to limit the invention in any way. All temperatures are in degrees Celsius.

Intermediate 1

(\pm)-Cis-2-hydroxymethyl-5-(5'-fluorocytosin-1'-yl)-1,3-oxathiolane

(i) 2-Benzoyloxymethyl-5-acetoxy-1,3-oxathiolane
Benzoyloxycetaldehyde (216.33 g, 1.32 mol) was dissolved in pyridine (373 ml, 4.61 mol) and 1,4-dithiane-2,5-diol (100.31 g, 0.66 mol) was added to the solution. The heterogenous mixture was stirred at 60°–65° C. under nitrogen atmosphere for 1 hour. At the end of the reaction, a complete solution was obtained. Dichloromethane (650 ml) was added to the reaction mixture and it was cooled to 0° C. with salt-ice bath. Acetyl chloride (281 ml, 3.95 mol) was added dropwise to the solution at 0–5° C. over 1.5–2 hours.

The reaction mixture was stirred at 0°–5° C. for 30 minutes, then it was poured carefully onto a cold (0°C.) solution of saturated sodium bicarbonate. The organic layer was separated. The water layer was extracted with dichloromethane (3×200 ml). The combined organic layers were washed with saturated sodium bicarbonate solution (3×200 ml) and brine (200 ml). The solution was dried over sodium sulfate and concentrated in vacuo. The traces of pyridine were removed by azeotropic distillation with benzene. 320.79 g crude product was obtained which was purified by Kugelrohr distillation or filtration through a short silica gel column. [Solvent system: hexane/ethyl acetate (3/1)].

(ii) *Cis*- and *trans*-2-benzoyloxymethyl-5-(N₄'-acetyl-5'-fluoro-cytosin-1'-yl)-1,3-oxathiolane.

5-Fluorocytosine (4.30 g, 33.3 mmol), hexamethyldisilazane (25 ml) and ammonium sulfate (120 mg) were boiled under reflux until the cytosine dissolved (3 hours) and then further refluxed for 2 hours. The hexamethyldisilazane was evaporated in vacuo and toluene (100 ml) was added to the residue to co-evaporate the solvents. The resulting solution bis(trimethylsilyl)-fluorocytosine in dichloromethane (40 ml) was added under argon to a solution of 2-benzoyloxymethyl-5-acetoxy-1,3-oxathiolane (8.537 g, 30.3 mmol) in dry dichloromethane (100 ml) and molecular sieves (4A, 2 g) previously prepared under argon and cooled at 0° C. for 20 minutes. [(Trifluoromethane-sulfonyl)oxy]trimethyl silane (6 ml, 31 mmol) was added to this mixture at 0° C. and the resulting solution was stirred at room temperature for 2 hours. The filtrate was shaken two times with 300 ml of brine and one time with distilled water. The organic layer was dried over magnesium sulfate, filtered and evaporated to dryness. This afforded a crude 5-fluoro-cytosine derivative (10.1 g). $R_f=0.57$ (EtOAc:MeOH 9:1).

This residue was acetylated in the next step without further purification. The crude material was dissolved in dry dichloromethane (120 ml) in a 500 ml round bottom flask under argon. Triethylamine (12.7 ml, 91.1 mmol) and dimethyl aminopyridine (111 mg, 0.9 mmol) were added to the solution. The flask was then immersed in an ice bath for 1 hour under argon. Acetic anhydride (4.3 ml, 45 mmol), distilled over sodium acetate, was syringed into the cooled flask. The mixture was stirred overnight and then carefully decanted into an erlenmeyer flask containing saturated sodium bicarbonate solution. The product was then washed with distilled water followed by brine solution. The methylene chloride portions were dried and evaporated under high vacuum to dryness, yielding an acetylated α/β mixture as a colorless foam, weighing 9.6 g after drying. Flash chromatography of this material using ethylacetate: methanol (9:1) afforded 3.1 g, 7.8 mmol (46%) pure *trans*- and 3.5 g, 8.9 mmol (30%) pure *cis*- title compounds.

trans-isomer: $R_f=0.65$ in ethyl acetate:methanol 9:1

U.V.: (MeOH) Lambda max: 309 nm

¹H-NMR δ (ppm in CDCl₃) 8.77 (b, 1H; C₄'—N H—Ac) 8.06 (m, 2H; aromatic) 7.70 (d, 1H; C₆'—H, $J_{CF}=6.3$ Hz) 7.62 (m, 1H; aromatic) 7.49 (m, 2H; aromatic) 6.51 (dd, 1H; C₅—H) 5.91 (dd, 1H; C₂—H) 4.48 (dd, 2H; C₂—CH₂OCOC₆H₅) 3.66 (dd, 1H; C₄—H) 3.34 (dd, 1H; C₄—H) 2.56 (s, 3H; NH—COCH₃)

cis-isomer: $R_f=0.58$ in ethyl acetate:methanol 9:1

U.V.: (MeOH) Lambda max: 309 nm

¹H-NMR δ (ppm in CDCl₃) 8.72 (b, 1H; C₄'—N H—Ac) 8.06 (m, 2H; aromatic) 7.87 (d, 1H; C₆'—H, $J_{CF}=6.2$ Hz) 7.60 (m, 1H; aromatic) 7.49 (m, 2H; aromatic) 6.32 (dd, 1H; C₅—H) 5.47 (dd, 1H; C₂—H) 4.73 (dd, 2H; C₂—CH₂OCOC₆H₅) 3.62 (dd, 1H; C₄—H) 3.19 (dd, 1H; C₄—H) 2.55 (s, 3H; NH—COCH₃)

(iii) (±)-Cis-hydroxymethyl-5-(5'-fluorocytosin-1'-yl)-1,3-oxathiolane.

1.2 g (3.05 mmol) of cis-2-benzoyloxymethyl-5-(N⁴-acetyl-5'-fluorocytosin-1'-yl)-1,3-oxathiolane was stirred in 30 ml of methanolic ammonia at 0° C. for 1 hour and then overnight at room temperature. The mixture was evaporated under reduced pressure. The residue was triturated twice (2×30 ml) with anhydrous ether. The solid residue was recrystallized in absolute ethanol to give 655 mg (2.64 mmol, 87%) of pure cis title product: m.p. 204°–206° C.; R_f=0.21 in ethylacetate:methanol (9:1). The desired compound was identified by ¹H, ¹³C-NMR and U.V. Lambda max (H₂O) 280.9 nm.

cis-isomer:

¹H-NMR δ (ppm in DMSO-d₆) 8.22 (d, 1H; C₆'-H, J_{CF}=7.26 Hz) 7.84 (d, 2H; C₄'-NH₂) 6.16 (t, 1H; C₅-H) 5.43 (t, 1H; C₂-CH₂-OH) 5.19 (t, 1H; C₂-H) 3.77 (m, 2H; C₂-CH₂OH) 3.35 (dd, 1H; C₄-H) ¹³C-NMR (DMSO-d₆)

C ₆ '	C ₂ '	C ₄ '	C ₅ '
153.46	158.14 (² J _{CF} = 14.0 Hz)	134.63 (J _{CF} = 24.1 Hz)	126.32 (J _{CF} = 32.5 Hz)
C ₅	C ₄	C ₂	CH ₂ OH
86.82	36.80	86.77	62.32

EXAMPLE 1

(-)-4-Amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one

(i) (±) Cis-2-hydroxymethyl-5-(5'-fluorocytosin-1'-yl)-1,3-oxathiolane monophosphate.

To a stirred mixture of Intermediate 1 (500 mg, 2.024 mmol) in dry trimethyl phosphate (10 ml) cooled to 0° C., was added dropwise phosphorus oxychloride (1.22 ml, 13.1 mmol). The reaction mixture was stirred at that temperature for 1 hour and then quenched in ice water. The pH of the cold mixture was adjusted to 3 by the addition of aqueous 1N sodium hydroxide, then applied to a charcoal column (5 g, DARCO), which was eluted with water followed by ethanol and aqueous ammonia in a (10:10:1) ratio. Fractions containing crude monophosphate were combined and evaporated and subsequently were applied to a column containing 15 g of DEAE sephadex A25 (HCO₃-form). Elution was undertaken with a gradient of water (300 ml), 0.1M-NH₄HCO₃ (300 ml), and 0.2M NH₄HCO₃ (100 ml). Evaporation of appropriate fractions after dilution with water (30 ml) afforded (±) cis-2-hydroxymethyl-5-(5'-fluorocytosin-1'-yl)-1,3-oxathiolane monophosphate as a white solid R_f=0.5 (n. PrOH:NH₄OH 6:4) yield=612 mg, 1.77 mmol, 87.9%. ¹H NMR δ (ppm in D₂O). 8.27 (d, 1H, C₆'-H, J_{H,F}=6.47 Hz), 6.33 (dd, 1H, C₅-H), 5.47 (t, 1H, C₂-H), 4.84 (m, 2H, C₂-CH₂OH), 3.63 (dd, 1H, C₄H), 3.30 (dd, 1H, C₄H). HPLC>99%.

(ii) (+)-Cis-2-hydroxymethyl-5-(5'-fluorocytosin-1'-yl)-1,3-oxathiolane.

To a solution of (±) cis-2-hydroxymethyl-5-(5'-fluorocytosin-1'-yl)-1,3-oxathiolane monophosphate (100 mg, 0.29 mmol) in 3 ml of glycine buffer solution [glycine (52.6 mg) and magnesium chloride (19 mg) in water (10 ml)], was added in one portion 5'-nucleotidase [Sigma, 3.5 mg at 29 unit/mg]. The resulting mixture was incubated at 37° C. with shaking. The reaction was monitored by HPLC [chiral

column α -acid glycoprotein (AGP) using 0.2M sodium phosphate as eluant at pH 7 with a flow rate 0.15 ml/min] at different intervals. Only the (+)-enantiomer was observed after 2.5 hours. More enzyme (2 mg) was added, and incubation was continued for a further 3 hours. HPLC analysis clearly showed selective and complete hydrolysis of the (+)-enantiomer. The resulting mixture was applied to a column of DEAE sephadex A-25 (HCO_3 form). Elution was undertaken with water (155 ml), followed by 0.1 and 0.2M NH_4HCO_3 (100 ml each). Appropriate fractions containing the first eluted nucleoside were combined and concentrated. The remaining solid was purified on a short column silica using ethyl acetate, methanol (4.5:0.5) as eluant and then separated by HPLC (employing the above mentioned conditions). This afforded pure (+)-cis-2-hydroxymethyl-5-(5'-fluorocytosin-1'-yl)-1,3-oxathiolane (23 mg, 0.093 mmol, 32%) as a white solid ($[\alpha]_D^{25} +123^\circ \text{C}$. [c, 1.00, MeOH]m.p. 185°C . NMR δ (ppm in DMSO). 8.26 (d, 1H, $\text{C}'_6\text{-H}$, $J_{\text{H-F}}=5.22 \text{ Hz}$), 7.87 (s, 1H, NH_2 , D_2O exchangeable), 7.63 (s, 1H, NH_2 , D_2O exchangeable), 6.20 (dd, 1H, $\text{C}_5\text{-H}$), 5.48 (t, 1H, $\text{C}_2\text{-H}$), 5.24 (t, 1H, $\text{CH}_2\text{-OH}$, D_2O exchangeable), 3.84 (m, 2H, $\text{C}_2\text{-CH}_2\text{OH}$), 3.50 (dd, 1H, $\text{C}_4\text{-H}$), 3.37 (dd, 1H, $\text{C}_4\text{-H}$).

(iii) (-)-Cis-2-hydroxymethyl-5-(5'-fluorocytosin-1'-yl)-1,3-oxathiolane

Appropriate fractions from the sephadex column containing the second eluted nucleoside described in step (ii) were combined and evaporated under reduced pressure. The residue was dissolved in 2 ml of water and treated with alkaline phosphatase (Sigma, 1 ml at 60 units/ml) followed by incubation at 37°C . for 1.5 hours. Solvent was then evaporated and the residue was purified by column chromatography on silica gel using EtOAc:MeOH (4:1) as eluent followed by HPLC (separation using the same conditions

mentioned above). This afforded pure (-)-cis-2-hydroxymethyl-5-(5'-fluorocytosin-1'-yl)-1,3-oxathiolane (20 mg, 0.081 mmol, 28%) m.p. 190°C . (d) $\text{rf}=0.21$, EtOAc:MeOH (4:1). U.V.: (H_2O) max: 279.1 nm. ^1H NMR δ (ppm in DMSO- d_6). 8.25 (d, 1H, $\text{C}'_6\text{-H}$, $J_{\text{H-F}}=7.26 \text{ Hz}$), 7.88 (b, 1H, $\text{C}'_4\text{-NH}_2$, D_2O exchangeable), 7.85 (b, 1H, $\text{C}'_4\text{-NH}_2$, D_2O exchangeable), 5.24 (t, 1H, $\text{C}_2\text{-H}$), 3.83 (m, 2H, $\text{C}_2\text{-CH}_2\text{-OH}$), 3.19 (dd, 1H, $\text{C}_4\text{-H}$), 3.15 (dd, 1H, $\text{C}_4\text{-H}$).

Intermediate 2 and Example 2 depict an alternate process for preparing the compound of formula (A).

Intermediate 2

(1'R,2'S,5'R)-MENTHYL-5R-(5'-
FLUOROCYTOSIN-1"-YL)-1,
3-OXATHIOLANE-2S-CARBOXYLATE

To a suspension of 5-fluorocytosine (155 mg, 1.2 mmol) in CH_2Cl_2 (1 mL) at room temperature under an argon atmosphere was added, successively, 2,4,6-collidine (0.317 mL, 2.4 mmol) and t-butyldimethylsilyl trifluoromethanesulfonate (0.551 mL, 2.4 mmol). The resultant mixture was stirred for 15 minutes and a clear solution was obtained. A solution of (1'R,2'S,5'R)-menthyl-5R-acetoxy-1,3-oxathiolane-2S-carboxylate (330 mg, 1 mmol) in CH_2Cl_2 (0.5 mL) was introduced, followed by iodotrimethylsilane (0.156 mL, 1.1 mmol). Stirring was continued for 3 hours. The mixture was diluted with CH_2Cl_2 (20 mL) and washed successively with saturated aqueous NaHSO_3 , water, brine and then was concentrated. The residue was taken up in ether-hexanes (1:1, 10mL) and saturated aqueous NaHCO_3 (2 mL) and stirred at room temperature for 15 minutes. The aqueous

layer was removed and the organic phase was centrifuged to afford a white solid which was washed with hexanes (3x5 mL) and then dried under vacuum. The product (1'R,2'S,5'R)-menthyl-5R-(5"-fluorocytosin-1"-yl)-1,3-oxathiolane-2S-carboxylate (350 mg, 88%) thus obtained contained about 6% of (1'R,2'S,5'R)-methyl-5S-(5"-fluorocytosin-1"-yl)-1,3-oxathiolane-2S-carboxylate (NMR). This material was recrystallized from MeOH/CH₂Cl₂/benzene to give a crystalline product: $[\alpha]_D^{26+22^\circ}$ (c, 0.19, MeOH); m.p. 216°-218° C., ¹H NMR (CDCl₃) δ 0.78 (d, 3H, J=7 Hz), 0.91 (t, 6H, J=7.3 Hz), 1.00 (m, 2H), 1.39-2.04 (m, 7H), 3.12 (dd, 1H, J=6.6 Hz, 6.1 Hz), 3.52 (dd, 1H, J=4.7 Hz, 6.1 Hz), 4.79 (dt, 1H, J=4.4 Hz, 4.3 Hz), 5.46 (s, 1H), 5.75 (bs, 1H, exchangeable), 6.42 (5t, 1H, J=5.0 Hz), 8.10 (bs, 1H, exchangeable), 8.48 (d, 1H, J=6.6 Hz); ¹³C NMR (CDCl₃, DMSO-d₆) δ 16.7, 21.2, 22.4, 23.7, 26.6, 31.8, 34.4, 36.6, 40.5, 47.2, 77.1, 79.1, 90.8, 126.3 (d, J=33 Hz), 137.1 (d, J=244 Hz), 154.2, 158.3 (d, J=15 Hz), 170.1.

EXAMPLE 2

2S-HYDROXYMETHYL-5R-(5'-FLUOROCYTOSIN-1'-YL)-1,3-OXATHIOLANE

To a suspension of lithium aluminum hydride (10 mg, 0.54 mmol) in THF (1 mL) at ambient temperature under an argon atmosphere was slowly added a solution of (1'R,2'S,5'R)-menthyl-5R-(5"-fluorocytosin-1"-yl)-1,3-oxathiolane-2S-carboxylate (54 mg, 0.135 mmol) in THF (2 mL). The reaction mixture was allowed to stir for 30 minutes, then quenched with excess methanol (2 mL), followed by the addition of silica gel (3 g). The resultant slurry was subjected to silica gel column chromatography (EtOAc-Hexane-MeOH, 1:1:1) to provide a gummy solid which was dried azeotropically with toluene to give 20.7 mg (63%) of a white solid as the product: $[\alpha]_D^{26+114^\circ}$ (c, 0.12, MeOH); ¹H NMR (DMSO-d₆) δ 3.14 (dd, 1H, J=4.3, 11.9 Hz), 3.42 (dd, 1H, J=5.3, 11.9 Hz), 3.76 (m, 2H), 5.18 (m, 1H), 5.42 (t, 1H, J=4.8 Hz), 6.14 (m, 1H), 7.59 (br m, 1H, exchangeable), 7.83 (br m, 1H, exchangeable), 8.20 (d, 1H, J=7.66 Hz).

EXAMPLE 3

Biological Activity

(i) Antiviral Activity

Antiviral activity of the compound of Example 1 was determined against HIV-1 in the following cell lines.

C8166 cells, a human T-lymphoblastoid cell line, infected with HIV-1 strain RF.

MT-4 cells, a human T-cell leukaemia cell line, infected with HIV-1 strain RF.

Antiviral activity in C8166 cells was determined by inhibition of syncytium formation (Tochikura et al Virology, 164, 542-546) and in MT-4 cells by inhibition of formazan conversion [Baba et al, *Biochem Biophys Res Commun.*, 142, pp. 128-134 (1987); Mossman, *J. Immun. Meth.*, 65, pp. 55-57 (1983)]. Antiviral activities were also determined by analyzing the amount of HIV p24 antigen synthesized in the presence and absence of enantiomers.

C. for 5 days, the viable cell count was determined by removing a sample of cell suspension and counting trypan blue excluding cells in a hemocytometer.

The results are shown in Table 3.

TABLE 3

Compound	50% Cytotoxicity ($\mu\text{g/ml}$)	
	CEM cells	H9 cells
(+)-enantiomer	217	334
(-)-enantiomer	148	296
Intermediate 1	173	232

I claim:

1. (-)-Cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one or a pharmaceutically acceptable salt, ester or salt of an ester thereof.

2. The substantially pure (-)-enantiomer of cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one or a pharmaceutically acceptable salt, ester or salt of an ester thereof, wherein the (+) enantiomer is present in an amount of no more than 5% w/w.

3. The compound of claim 2 wherein the (+)-enantiomer is present in an amount of no more than about 2% w/w.

4. The compound of claim 2 wherein the (+)-enantiomer is present in an amount of less than about 1% w/w.

5. A pharmaceutical composition comprising a compound as in any one of claims 1, 2, 3, or 4 in combination with a pharmaceutically acceptable carrier.

6. A compound according to claim 1, wherein said compound is a pharmaceutically acceptable ester of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one wherein the 2-hydroxymethyl group is replaced by R-CO- and R is H, straight or branched chain alkyl, alkoxyalkyl, aryloxyalkyl, alkylsulphonyl or aralkylsulphonyl, in which alkyl moieties have 1-16 carbon atoms and aryl is phenyl.

7. A compound according to claim 1, wherein said compound is a pharmaceutically acceptable ester of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one wherein the 2-hydroxymethyl group is replaced by an amino acid ester, a monophosphate ester, a diphosphate ester, or a triphosphate ester.

8. A compound according to claim 1, wherein said compound is a pharmaceutically acceptable ester of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one wherein the 2-hydroxymethyl group is replaced by R-CO- and R is H, methyl, ethyl, n-propyl, t-butyl, n-butyl, methoxymethyl, benzyl, phenoxymethyl, phenyl, or phenyl substituted by halogen, C₁₋₄ alkyl or C₁₋₄ alkoxy.

9. A compound according to claim 1, wherein said compound is a pharmaceutically acceptable ester of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one and said ester is a C₁₋₁₆ alkyl ester, an unsubstituted benzyl ester, or a benzyl ester substituted by at least one bromo, chloro, fluoro, iodo, C₁₋₄ alkyl, C₁₋₆ alkoxy, nitro or trifluoromethyl.

10. A compound according to claim 1, wherein said compound is (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one or a pharmaceutically acceptable salt thereof.

11. A compound according to claim 10, wherein said compound is a pharmaceutically acceptable salt of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one and said salt is derived from hydrochloric acid, hydrobromic, sulphuric acid, nitric acid, perchloric acid, fumaric acid, maleic acid, phosphoric acid, glycolic acid, lactic acid, salicylic acid, succinic acid, toluene-

p-sulphonic acid, tartaric acid, acetic acid, citric acid, methane sulphonic acid, formic acid, benzoic acid, malonic acid, naphthalene-2-sulphonic acid, benzene sulphonic acid, alkali metals, alkaline earth metals, ammonium, and NR_4^+ , in which R is C_{1-4} alkyl.

12. A compound according to claim 10, wherein said compound is (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one.

13. A compound according to claim 2, wherein said compound is a pharmaceutically acceptable ester of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one wherein the 2-hydroxymethyl group is replaced by R-CO- and R is H, straight or branched chain alkyl, alkoxyalkyl, aryloxyalkyl, alkylsulphonyl or aralkylsulphonyl, in which alkyl moieties have 1-16 carbon atoms and aryl is phenyl.

14. A compound according to claim 2, wherein said compound is a pharmaceutically acceptable ester of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one wherein the 2-hydroxymethyl group is replaced by an amino acid ester, a monophosphate ester, a diphosphate ester, or a triphosphate ester.

15. A compound according to claim 2, wherein said compound is a pharmaceutically acceptable ester of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one wherein the 2-hydroxymethyl group is replaced by R-CO- and R is H, methyl, ethyl, n-propyl, t-butyl, n-butyl, methoxymethyl, benzyl, phenoxymethyl, phenyl, or phenyl substituted by halogen, C_{1-4} alkyl or C_{1-4} alkoxy.

16. A compound according to claim 2, wherein said compound is a pharmaceutically acceptable ester of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one and said ester is a C_{1-16} alkyl ester, an unsubstituted benzyl ester, or a benzyl ester substituted by at least one bromo, chloro, fluoro, iodo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro or trifluoromethyl.

17. A compound according to claim 2, wherein said compound is (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one or a pharmaceutically acceptable salt thereof.

18. A compound according to claim 17, wherein said compound is a pharmaceutically acceptable salt of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one and said salt is derived from hydrochloric acid, hydrobromic, sulphuric acid, nitric acid, perchloric acid, fumaric acid, maleic acid, phosphoric acid, glycolic acid, lactic acid, salicylic acid, succinic acid, toluene-p-sulphonic acid, tartaric acid, acetic acid, citric acid, methane sulphonic acid, formic acid, benzoic acid, malonic acid, naphthalene-2-sulphonic acid, benzene sulphonic acid, alkali metals, alkaline earth metals, ammonium, and NR_4^+ , in which R is C_{1-4} alkyl.

19. A compound according to claim 17, wherein said compound is (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one.

20. A compound according to claim 3, wherein said compound is a pharmaceutically acceptable ester of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one wherein the 2-hydroxymethyl group is replaced by R-CO- and R is H, straight or branched chain alkyl, alkoxyalkyl, aryloxyalkyl, alkylsulphonyl or aralkylsulphonyl, in which alkyl moieties have 1-16 carbon atoms and aryl is phenyl.

21. A compound according to claim 3, wherein said compound is a pharmaceutically acceptable ester of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one wherein the 2-hydroxymethyl group is replaced by an amino acid ester, a monophosphate ester, a

22. A compound according to claim 3, wherein said compound is a pharmaceutically acceptable ester of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl)-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one wherein the 2-hydroxymethyl group is replaced by R-CO- and R is H, methyl, ethyl, n-propyl, t-butyl, n-butyl, methoxymethyl, benzyl, phenoxymethyl, phenyl, or phenyl substituted by halogen, C₁₋₄ alkyl or C₁₋₄ alkoxy.

24. A compound according to claim 3, wherein said compound is (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one or a pharmaceutically acceptable salt thereof.

26. A compound according to claim 24, wherein said compound is (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one.

28. A compound according to claim 4, wherein said compound is a pharmaceutically acceptable ester of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl)-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one wherein the 2-hydroxymethyl group is replaced by an amino acid ester, a monophosphate ester, a diphosphate ester, or a triphosphate ester.

30. A compound according to claim 4, wherein said compound is a pharmaceutically acceptable ester of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl)-1,3-oxathiolan-5-yl)- (1H)-pyrimidin-2-one and said ester is a C₁₋₁₆ alkyl ester, an unsubstituted benzyl ester, or a benzyl ester substituted by at least one bromo, chloro, fluoro, iodo, C₁₋₆ alkyl, C₁₋₆ alkoxy, nitro or trifluoromethyl.

32. A compound according to claim 31, wherein said

compound is a pharmaceutically acceptable salt of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one and said salt is derived from hydrochloric acid, hydrobromic, sulphuric acid, nitric acid, perchloric acid, fumaric acid maleic acid phosphoric acid, glycolic acid, lactic acid salicylic acid, succinic acid, toluene-p-sulphonic acid, tartaric acid, acetic acid, citric acid, methane sulphonc acid, formic acid, benzoic acid, malonic acid, naphthalene-2-sulphonic acid, benzene sulphonc acid, alkali metals, alkaline earth metals, ammonium, and NR_4^+ , in which R is C_{1-4} alkyl.

33. A compound according to claim 32, wherein said compound is (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one.

34. A composition comprising the (-)-enantiomer of cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable ester thereof, or a pharmaceutically acceptable salt of an ester thereof, and

the corresponding (+) enantiomer, wherein said (+) enantiomer is present in an amount of no more than 5% w/w.

35. A composition according to claim 34, wherein said composition comprises a pharmaceutically acceptable ester of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one wherein the 2-hydroxymethyl group is replaced by R-CO- and R is H, straight or branched chain alkyl, alkoxyalkyl, aryloxyalkyl, alkylsulphonyl or aralkylsulphonyl, in which alkyl moieties have 1-16 carbon atoms and aryl is phenyl.

36. A composition according to claim 34, wherein said composition comprises a pharmaceutically acceptable ester of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one wherein the 2-hydroxymethyl group is replaced by an amino acid ester, a monophosphate ester, a diphosphate ester, or a triphosphate ester.

37. A composition according to claim 34, wherein said composition comprises a pharmaceutically acceptable ester of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one wherein the 2-hydroxymethyl group is replaced by R-CO- and R is H, methyl, ethyl, n-propyl, t-butyl, n-butyl, methoxymethyl, benzyl, phenoxymethyl, phenyl, or phenyl substituted by halogen, C_{1-4} alkyl or C_{1-4} alkoxy.

38. A composition according to claim 34, wherein said composition comprises a pharmaceutically acceptable ester of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one and said ester is a C_{1-16} alkyl ester, an unsubstituted benzyl ester, or a benzyl ester substituted by at least one bromo, chloro, fluoro, iodo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro or trifluoromethyl.

39. A composition according to claim 34, wherein said composition comprises (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one or a pharmaceutically acceptable salt thereof.

40. A composition according to claim 39, wherein said composition comprises a pharmaceutically acceptable salt of (-)-cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one and said salt is derived from hydrochloric acid, hydrobromic, sulphuric acid, nitric acid, perchloric acid, fumaric acid maleic acid phosphoric acid, glycolic acid, lactic acid salicylic acid, succinic acid, toluene-p-sulphonic acid, tartaric acid, acetic acid, citric acid, methane sulphonc acid, formic acid, benzoic acid, malonic acid, naphthalene-2-sulphonic acid, benzene sulphonc acid, alkali metals, alkaline earth metals, ammonium, and NR_4^+ , in which R is C_{1-4} alkyl.

41. A composition according to claim 39, wherein said composition comprises(-) -cis-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one.

5 42. A composition according to claim 34, wherein said (+)-enantiomer is present in an amount of no more than 2% w/w.

43. A composition according to claim 35, wherein said (+)-enantiomer is present in an amount of no more than 2% w/w.

10 44. A composition according to claim 36, wherein said (+)-enantiomer is present in an amount of no more than 2% w/w.

45. A composition according to claim 37, wherein said (+)-enantiomer is present in an amount of no more than 2% w/w.

15 46. A composition according to claim 38, wherein said (+)-enantiomer is present in an amount of no more than 2% w/w.

20 47. A composition according to claim 39, wherein said (+)-enantiomer is present in an amount of no more than 2% w/w.

48. A composition according to claim 40, wherein said (+)-enantiomer is present in an amount of no more than 2% w/w.

25 49. A composition according to claim 41, wherein said (+)-enantiomer is present in an amount of no more than 2% w/w.

50. A composition according to claim 34, wherein said (+)-enantiomer is present in an amount of no more than 1% w/w.

30 51. A composition according to claim 35, wherein said (+)-enantiomer is present in an amount of no more than 1% w/w.

35 52. A composition according to claim 36, wherein said (+)-enantiomer is present in an amount of no more than 1% w/w.

53. A composition according to claim 37, wherein said (+)-enantiomer is present in an amount of no more than 1% w/w.

40 54. A composition according to claim 38, wherein said (+)-enantiomer is present in an amount of no more than 1% w/w.

55. A composition according to claim 39, wherein said (+)-enantiomer is present in an amount of no more than 1% w/w.

45 56. A composition according to claim 40, wherein said (+)-enantiomer is present in an amount of no more than 1% w/w.

50 57. A composition according to claim 41, wherein said (+)-enantiomer is present in an amount of no more than 1% w/w.

58. A composition according to claim 5, wherein said composition contains 10-1500 mg of said compound.

55 59. A composition according to claim 58, wherein said composition contains 20-1000 mg of said compound.

60. A composition according to claim 59, wherein said composition contains 50-700 mg of said compound.

60 61. A pharmaceutical composition comprising a compound as in any one of claims 6-33 in combination with a pharmaceutically acceptable carrier.

62. A composition according to claim 61, wherein said composition contains 10-1500 mg of said compound.

63. A composition according to claim 62, wherein said composition contains 20-1000 mg of said compound.

65 64. A composition according to claim 63, wherein said composition contains 50-700 mg of said compound.

65. A composition according to claim 34, further comprising a pharmaceutically acceptable carrier.

66. A composition according to claim 65, wherein said

composition contains 10-1500 mg of said compound.

67. A composition according to claim 66, wherein said composition contains 20-1000 mg of said compound.

5 68. A composition according to claim 67, wherein said composition contains 50-700 mg of said compound.

* * * * *

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reissue Application of : Box: REISSUE
Gervais DIONNE et al. : Group Art Unit:
Original U.S. Patent No. 5,538,975
Serial No.: Not Yet Issued : Examiner: James O. Wilson
Filed: Herewith :
For: **1,3-OXATHIOLANE NUCLEOSIDE ANALOGUES AND METHODS FOR
USING SAME**

**POWER OF ATTORNEY, OATH and
REISSUE DECLARATION UNDER 37 C.F.R. §1.175 and § 1.63**

Assistant Commissioner for Patents
Washington, D.C. 20231

SIR:

The undersigned inventors of the subject matter of the claims of U.S. Patent No. 5,538,975 and of the subject matter of the claims as proposed herein for reissue, being duly warned, declare as follows:

The undersigned inventors of the subject matter of the claims of U.S. Patent No. 5,538,975 and of the subject matter of the claims as proposed herein for reissue, believe their original patent U.S. Patent No. 5,538,975 to be wholly or partly inoperative by reason of the patentees claiming less than they had a right to claim in the patent. Specifically, there is an error in that the patent does not contain claims of intermediate scope, i.e., narrower in scope than at least one claim of the issued patent. Also, there is an error in that the inventive entity is incorrectly indicated as Gervais Dionne and should instead be Gervais Dionne, Bernard Belleau, Nghe Nguyen-Ba, and Boulos Zacharie. Further, there is an error in that the patent does not include a claim to priority under co-pending application Serial No. 07/564,160, filed August 8, 1990, which also discloses the (-)-enantiomer of *cis*-2-hydroxymethyl-5-(5'-fluorocytosin-1'-yl)-1,3-oxathiolane.

All errors sought for correction by this reissue application up to the filing of this reissue oath arose without any deceptive intention on the part of Applicants.

We have reviewed and understand the contents of the specification, including the claims, as amended in the attached reissue application.

We believe the named inventors to be the original and first inventors of the subject matter which is claimed and for which a patent is sought.

We acknowledge the duty to disclose all information known to the Applicants to be material to patentability as defined by 37 C.F.R. §1.56.

We hereby appoint as our attorneys with power of substitution and revocation to transact all business in the Patent and Trademark Office connected therewith:

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We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

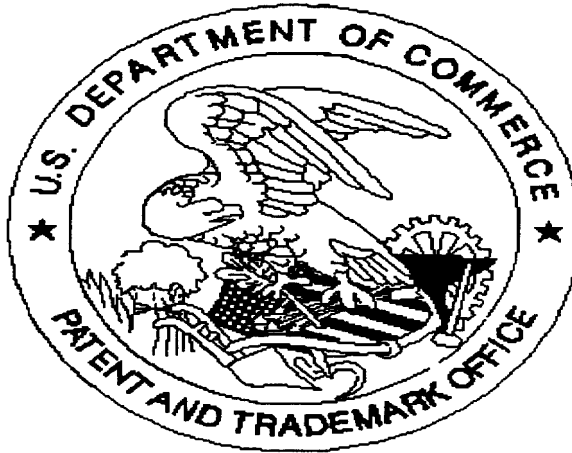
Date Gervais DIONNE

Date Nghe NGUYEN-BA

Date Boulos ZACHARIE

Date Bernard BELLEAU (deceased), by Pierette Belleau,
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